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Where Are We Now?

In the current study, Collier and colleagues [5] describe an in-vitro drug-screening approach to evaluate micrometastatic disease in osteosarcoma. They generated sarcospheres using established human osteosarcoma cell lines with metastatic potential and found an individual response upon methotrexate, doxorubicin, and cisplatin (MAP) treatment.

There is a desperate need to improve treatment strategies in patients with metastatic osteosarcoma. Five-year event-free survival of patients with localized osteosarcoma is approximately 70%, but that number drops to around 20% for those with metastatic disease. For this reason, the work of Collier and colleagues is important.

A conventional drug-development path requiring drugs to induce regression of established lesions has not led to improvements of survival during the last 30 years. Because metastasis is often fatal, it is essential that we focus on developing therapeutics that target metastatic progression [12]. To do so, we heavily depend on cancer modeling, although all models have limitations and are imperfect representations of real systems [21]. Drug screeening using commercially available cell lines is hampered by considerable genomic instability during cell culture due to gene expression and chromosomal abberrations [14]. By allowing the interaction of osteosarcoma cells and extracellular matrix, three-dimensional (3-D) in vitro models offer a clear advantage over 2-D models. This interaction regulates the proliferation and differentiation in space and time, and helps identify the role of proteins involved in the metastatic behavior [19]. In vivo sarcoma models are divided into spontaenous models (for example, dogs that develop osteosarcomas) and induced models (such as syngenic mouse models). Syngenic mouse models are distinguished from xenografts, whereby the specific inoculation of patient-derived tumor material is referred as patient-derived xenografts. Such models, each with its limitations, have been refined over the years and have good predictive value [15, 16]. But because of a general lack of changes to survivorship over time in patients with osteosarcoma despite these laboratory efforts, clincial trials are absolutely instrumental and have to be supported for patients with osteosarcoma [10]. On the other hand, stringent inclusion criteria cannot be emphasized enough, and differences in these criteria may explain the fact that survival of patients with localized osteosarcoma has not improved in the last three decades [11]. Therefore, 3-D sarcospheres focusing on the metastatic cascade using patient-derived tumor material will

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be a necessary step to define new targets.

Where Do We Need To Go?

In this context, a rational progression from preclinical studies using in-vitro cell lines in combination with in vivo mouse/dog model approaches must be developed. As Collier and colleagues noted in their study, the establishment of in vitro 3-D cellular cultures of tumor cells (known as organoids) may represent the basis for high-throughput drug screening to identify molecules that limit cancer-cell growth. Such a drug would then be used in patient-derived xenograft models to generate possible treatment options, before being used as a tumor precision approach in clinical trials [7].

The goal is to improve the survival of patients with osteogenic sarcoma using a personalized drug approach. Collier and colleagues [5] focused on metastasis and noted that sarcospheres are just a starting point, and several challenging issues still need to be confronted. First, to develop drug combinations against metastases, we will likely need to target several steps of the process that lead to metastases, including genetic mutations and protein expression. But the problem goes well beyond those elements, and so we need also to focus attention on epigenetic factors, metabolic abnormalities, the immunolgy of cancer, the microenvironments in which tumors reside, and how tumor cells enter the bloodstream [18]. It is unlikely that a singular genetic alteration (such as in gastrointestinal stromal tumor) can be successfully targeted, and combinations of several targets have to be envisaged, adding a tremendous complexity to define treatment success.

Second, next-generation sequencing by delineating the genomic landscape of individual tumors will greatly impact the future of cancer therapy. But this kind of research is challenging. For example, each sequence analysis captures only one moment in time, while cancer is continuously evolving and adapting [21], which helps explain the recently recognized intratumoral heterogeneity [8, 20], as well as the need for novel drug therapies [4]. If multiple biopsies of one single tumor share only one-third of all mutations being present in the respective tumor [8], one might question how representative an ex-vivo analysis for drug screening may be. This is particularly important for patients with osteosarcoma, where the biopsy to establish the diagnosis is followed by neoadjuvant chemotherapy, before complete surgical resection.

Finally, based on the action of new anticancer agents with greater molecular specificity, we may have to introduce new rules for developing drug combinations. Instead of additive or synergistic treatment responses, drug combinations may be effective via independent activities of the individually administered drugs. Therefore, a better understanding of signaling networks is imperative for combination regimens [17]. Further, a treatment response is usually assessed by progression free survival and/or tumor necrosis rate. Considering the dynamics of cancer therapies, the kill rate and progression-free survival are not sufficient measures for long-term cancer control; instead, time to tumor regrowth may be more accurate [3].

How Do We Get There?

Most oncology drugs come onto the market without clear evidence that they improve overall survival or a patient's quality of life. And if a benefit is shown, then it's not always meaningful [6]. Applying stringent criteria with robust preclinical evidence before performing clinical trials is absolutely necessary [11].

Because metastasis is the primary cause of death, the effectiveness of any therapy can only be measured by the ability to interfere with this event. Metastatic tumor cells (or circulating tumor cells), which can be collected from the peripheral blood, allow for the early detection of tumor status, which is the key. Circulating tumor cells from liquid biopsies—through the analysis of the unique cancer cells' protein or oncogenic mutations and epigenetic changes—allow for the assessment of genetic evolution to adapt to any treatment [1, 13]. Further, identifying protein biomarker signatures from the blood may, simultaneously allow precision diagnostics to detect the disease as early as possible [2].

Should these approaches generate a wealth of data, international and interdisciplinary collaboration of numerous groups would be needed. The development of the High Dimensional Data platform—a relational biologic database derived from matched osteosarcoma biospecimens in which diverse experimental readouts were generated and digitally deposited [9]—promotes in silico hypothesis testing in sarcoma biology, and may represent an invaluable step forward to improve the overall survival of patients with osteosarcoma.

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